PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RG/G-33571A/LEK	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/SI2004/000044	International filing date *(day/month/year)* 22.12.2004	Priority date *(day/month/year)* 23.12.2003
International Patent Classification (IPC) or national classification and IPC INV. A61K9/16 A61K31/18 A61P13/08		
Applicant LEK PHARMACEUTICALS D.D. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.12.2005	17.05.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Vermeulen, S Telephone No. +49 89 2399-7520

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SI2004/000044

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-10 as originally filed

   Claims, Numbers

   1-15 filed with the demand

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has, within the applicable time limit:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest and, where applicable, the protest fee.

   ☐ paid additional fees under protest but the applicable protest fee was not paid.

   ☐ neither restricted the claims nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	13,15
	No:	Claims	1-12,14
Inventive step (IS)	Yes:	Claims	13,15
	No:	Claims	1-12,14
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item IV

Lack of unity of invention

The present set of claims comprises two inventions which are not so linked as to form a single general inventive concept:

1. Claims 1-5, 11-15: controlled release pellets characterized by a specific core matrix formulation

2. Claims 6-10: controlled release pellets characterized by a specific coating layer formulation

The groups of claims do not have common or corresponding special technical features making a possible contribution over the state of the art.

The only common subject-matter between invention 1 and 2 is the pellet core itself (cf. claims 2-5). This subject-matter, however, is not novel, since disclosed e.g. in US 6,602,522 and WO 92/10173. Accordingly, no common or corresponding special technical feature can be found between the subject-matter of claims 6-10 (directed to a specific coating) and the remaining claims, thus leading to non-unity of invention.

Furthermore, the groups of claims provide a different technical solution to the problem of controlling the release of a therapeutic agent:

1. Claims 1-5, 11-15: controlled release by specific design of the core matrix

2. Claims 6-10: controlled release by specific design of the coating layer

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document/s/:

D1: WO 92/10173 A (SMITHKLINE BEECHAM CORPORATION) 25 June 1992
D2: US-B1-6 602 522 (CHEN CHIH-MING ET AL) 5 August 2003
D3: DE 202 19 293 U1 (SYNTHON B.V., NIJMEGEN) 5 June 2003
D4: US 2003/147948 A1 (SHINODA TATSUKI ET AL) 7 August 2003
D5: US 2003/224050 A1 (CHIAO CHARLES ET AL) 4 December 2003
D6: US-A-5 041 430 (ADDICKS ET AL) 20 August 1991
D7: US 2003/077323 A1 (RUDNIC EDWARD M ET AL) 24 April 2003
D8: US-A-5 711 967 (JUCH ET AL) 27 January 1998

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-11 is not novel in the sense of Article 33(2) PCT. It should be noted that the relative terms "*low dose*" and "*freely soluble in water*" used in the said claims do not have a well-recognised meaning in terms of absolute values. For the question of novelty, said terms are accordingly considered in a broad sense.

The pellet cores defined in claims 1-5 and 11 are anticipated by D2 (e.g. example 2), which discloses controlled release granules comprising Eudragit NE and a surfactant (polysorbate). The granules are subsequently compressed into tablets.

The coated pellets defined in claims 6-10 are not novel over prior art disclosures which can be taken from e.g. D4-D8. Said documents disclose (cf. passages cited in the ISR) the combination of a polymer with pH dependent solubility (e.g. Eudragit L) and a polymer with pH independent solubility (e.g. Eudragit NE) in the preparation of an enteric sustained release coating. Said coating is applied on drug loaded cores (e.g. granules, pellets, microtablets). D4-D7 disclose the both polymer types in one single layer, whereas D8 discloses the polymers in two separate consecutive layers.

The subject-matter of claims 12 and 14 is not considered to involve an inventive step (Art. 33(3) PCT) in view of prior art disclosed in D1. Extrusion and spheronization of a matrix comprising an insoluble permeable polymer, such as Eudragit NE, is disclosed in D1 (cf. passages cited in the ISR), for the manufacture of extended release pellet cores. The subject-matter of D1 differs from the above mentioned claims only in that it does not explicitly mention the presence of a surfactant. Addition of a surfactant, however, is not considered to involve an inventive step, since it is taught on page 9 of D1 (cf. lines 24-28).

It is furthermore noted that it is a common practice to use surfactants, such as Tween (Polysorbate), when applying polyacrylate suspensions (e.g. Eudragit series) for improved processing and increased elasticity of the polymer matrix.

Claims 13 and 15 are directed specifically to the extended release of tamsulosin. Controlled release formulations of tamsulosin are known in the art and disclosed e.g. in D3. Controlled release in D3 is provided by a pellet core matrix comprising an acrylic polymer with pH-dependent solubility together with a coating layer consisting of the same acrylic polymer used in the pellet core. D3 also suggests to add HPMC in order to provide pH-independent release of tamsulosin in combination with the pH-dependent release. D3, however, does not suggest to formulate the core matrix with an insoluble permeable acrylic polymer as defined in the present application (cf. claim 4). Also, the document does not contain indications which would incite a skilled person to modify the pellet core and e.g. replace HPMC by the presently claimed insoluble acrylic polymer. Hence, the subject-matter of claims 13 and 15 is considered to provide a novel and inventive alternative tamsulosin delivery formulation (Art. 33(2)(3) PCT).

The subject-matter of claims 1-15 is considered to be industrially applicable and accordingly meets the requirements of Art.33(4) PCT.

Re Item VIII

Certain observations on the international application

Claim 1 lacks clarity (Article 6 PCT), because an attempt is made to define the product by reference to a result to be achieved, namely the controlled release of a low dose active substance from a pellet core in a controlled manner independently from pH.
The claim covers all products having this property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such products. This lack of support in the present case is such as to render a meaningful search and examination over the whole of the claimed scope impossible. Consequently, the search and examination have been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to a pellet core wherein the insoluble permeable polymer is a

copolymer of ethylacrylate and methylmethacrylate in a ratio of 2:1 (cf. claim 4) and to a pellet coating comprising a polymer soluble at pH>5.5 and a polymer with pH independent solubility (cf. claim 9 and 10).

CLAIMS

1. A controlled release pharmaceutical formulation of a low dose active substance freely soluble in water characterised in that it comprises a pellet core from which said active substance is released in a controlled manner independently from pH of the environment.
2. The pharmaceutical formulation according to claim 1 characterised in that said pellet core comprises at least one insoluble permeable polymer and at least one surfactant and optionally other excipients.
3. The pharmaceutical formulation according to claim 2 wherein said insoluble permeable polymer is selected from the group of acrylic polymers or alkyl celluloses or hydroxyalkyl celluloses or a combination thereof.
4. The pharmaceutical formulation according to claim 3 wherein said insoluble permeable polymer is a copolymer of ethylacrylate and methylmethacrylate in a ratio of 2:1, optionally being in the form of a 30 % aqueous dispersion.
5. The pharmaceutical formulation according to claims 1-4 wherein the diameter of the pellet cores is from about 0.5 to about 1.25 mm.
6. The pharmaceutical formulation according to claims 1-5 wherein said pellet core is coated with a gastroresistant and/or release controlling coating.
7. The pharmaceutical formulation according to claim 6 wherein the mass of the applied coating is from about 5 to about 10 % relative to the mass of dried pellet cores.
8. The pharmaceutical formulation according to claim 7 wherein the mass of the applied coating is from about 5 to about 8 % relative to the mass of dried pellet cores.
9. The pharmaceutical formulation according to claims 6-8 wherein the coating comprises at least one polymer soluble at pH values higher than about 5.5 and at least one polymer with a pH independent solubility.
10. The pharmaceutical formulation according to claim 9 wherein said polymer soluble at higher pH values is an anionic copolymer of methacrylic acid and ethylacrylate and said polymer with pH independent solubility is a copolymer of ethylacrylate and methylmethacrylate.
11. The pharmaceutical formulation according to claims 1-10 wherein the pellets are filled into capsules or sachets or compressed into tablets.

12. The pharmaceutical formulation according to claims 1-11 wherein the pellet cores are prepared by using the methods of extrusion and spheronization.
13. The pharmaceutical formulation according to any of the preceding claims wherein the freely soluble low-dose active substance is tamsulosin or a pharmaceutically acceptable salt thereof.
14. A process for the preparation of pharmaceutical formulations according to claims 1-13 characterised in that it comprises the following steps: preparation of the blend of the ingredients for the core, granulation, extrusion and spheronization, drying and optionally coating.
15. Use of the pharmaceutical formulation according to claim 13 for the preparation of a medicament for the treatment of benign prostatic hyperplasia.